IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	J. Varner	
Serial No.:	10/573,944	Group No.: 1644
Filed:	04/23/2007	Examiner: Michail A. Belyavskyi
Entitled:	**METHODS FOR ALTERING HEMATOPOIETIC PROGENITOR CELL ADHESION, DIFFERENTIATION, AND MIGRATION**	

RESPONSE TO SEPTEMBER 22, 2011 FINAL OFFICE ACTION

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Examiner Belyavskyi:

This is responsive to the above-referenced final Office Action, and is timely filed within the 3-month shortened statutory period ending after December 22, 2011. Accordingly, a request and fee for an extension of time are not enclosed. Enclosed as part of this response are

- Request for Continued Examination and fee, and
- Declaration under 37 C.F.R. §1.132 by Dr. David Cheresh, and *Curriculum Vitae*.

While the claims are not currently amended, a listing of the claims is nonetheless included, for the Examiner's convenience, beginning on page 2.

Remarks begin on page 7.

PENDING CLAIMS

1. **(Previously presented)** A method for detecting an altered level of hematopoietic progenitor cell adhesion to target tissue, comprising:

a) providing:

i) a population of cells comprising hematopoietic progenitor cells that express integrin $\alpha 4\beta 1$,

ii) target tissue that is not bone marrow endothelial tissue, and

iii) one or more agent that alters specific binding of integrin $\alpha 4\beta 1$ to an integrin $\alpha 4\beta 1$ ligand,

b) treating one or more of said population of cells and said target tissue with said agent under conditions for specific binding of said integrin $\alpha 4\beta 1$ with said integrin $\alpha 4\beta 1$ ligand, and

c) detecting an altered level of adhesion of said hematopoietic progenitor cells to said target tissue that is not bone marrow endothelial tissue.

2. **(Original)** The method of Claim 1, wherein said treating further comprises altering the level of trans-endothelial migration of said hematopoietic progenitor cells.

3. **(Original)** The method of Claim 1, wherein said treating further comprises altering the level of differentiation of said hematopoietic progenitor cells into a second cell type.

4. **(Original)** The method of Claim 3, wherein said second cell type is not a bone marrow endothelial cell.

5. **(Original)** The method of Claim 4, wherein said second cell type comprises one or more of mesenchymal cell, epithelial cell, muscle cell, neuronal cell, immune cell, melanocyte cell, myoepithelial cell, and embryonic cell.

6. **(Original)** The method of Claim 1, wherein said target tissue comprises one or more of vascular endothelial, muscle, neuronal, tumor, inflammatory, peripheral blood, cord blood, heart, ocular, skin, synovial, tumor, lung, breast, prostate, cervical, pancreatic, colon, ovarian, stomach,

esophageal, mouth, tongue, gum, skin, liver, bronchial, cartilage, testis, kidney, endometrium, uterus, bladder, spleen, thymus, thyroid, brain, neuron, gall bladder, ocular, and joint tissues.

7. **(Original)** The method of Claim 1, wherein said tissue is injured.

8. **(Original)** The method of Claim 1, wherein said tissue is ischemic.

9. **(Original)** The method of Claim 1, wherein said target tissue comprises fibronectin.

10. **(Original)** The method of Claim 1, wherein said target tissue comprises vascular tissue.

11. **(Original)** The method of Claim 1, wherein said treating is *in vitro*.

12. **(Original)** The method of Claim 1, wherein said treating is *in vivo* in a mammalian subject.

13. **(Original)** The method of Claim 12, wherein said mammalian subject is chosen from one or more of a subject that has a disease, is susceptible to having a disease, is suspected of having a disease, and is suspected of being susceptible to having a disease.

14. **(Original)** The method of Claim 13, wherein said mammalian subject is human.

15. **(Original)** The method of Claim 13, wherein said disease is angiogenic.

16. **(Original)** The method of Claim 13, wherein said disease is not angiogenic.

17. **(Original)** The method of Claim 1, wherein said agent comprises an antibody.

18. **(Original)** The method of Claim 17, wherein said antibody comprises an anti-integrin $\alpha 4\beta 1$ antibody.

19. **(Original)** The method of Claim 17, wherein said antibody comprises an anti-vascular cell adhesion molecule antibody.

20. **(Original)** The method of Claim 17, wherein said antibody comprises an anti-fibronectin antibody.

21. **(Original)** The method of Claim 1, wherein said ligand comprises vascular cell adhesion molecule (VCAM).

22. **(Original)** The method of Claim 1, wherein said ligand comprises fibronectin.

23. **(Withdrawn)** A method for screening a test compound for altering the level of hematopoietic progenitor cell adhesion to target tissue that is not bone marrow endothelial tissue, comprising:

a) providing:
   i) a first composition comprising integrin $\alpha4\beta1$,
   ii) a second composition comprising one or more integrin $\alpha4\beta1$ ligand, and
   iii) a test compound,

b) contacting said test compound with one or more of said first composition and said second composition under conditions for specific binding of said integrin $\alpha4\beta1$ with said integrin $\alpha4\beta1$ ligand, and

c) detecting an altered level of specific binding of said integrin $\alpha4\beta1$ with said integrin $\alpha4\beta1$ ligand in the presence of said test compound compared to in the absence of said test compound, thereby identifying said test compound as alerting the level of hematopoietic progenitor cell adhesion to said target tissue.

24. **(Withdrawn)** The method of Claim 23, wherein said method further comprises identifying said test compound as altering the level of trans-endothelial migration of said hematopoietic progenitor cells.

25. **(Withdrawn)** The method of Claim 23, wherein said method further comprises identifying said test compound as altering the level of differentiation of said hematopoietic progenitor cells to a second cell type.

26. **(Withdrawn)** The method of Claim 25, wherein said second cell type is not a bone marrow endothelial cell.

27. **(Withdrawn)** The method of Claim 26, wherein said second cell type comprises one or more of mesenchymal cell, epithelial cell, muscle cell, neuronal cell, immune cell, melanocyte cell, myoepithelial cell, and embryonic cell.

28. **(Withdrawn)** The method of Claim 23, wherein said target tissue comprises one or more of vascular endothelial, muscle, neuronal, tumor, inflammatory, peripheral blood, cord blood, heart, ocular, skin, synovial, tumor, lung, breast, prostate, cervical, pancreatic, colon, ovarian, stomach, esophageal, mouth, tongue, gum, skin, liver, bronchial, cartilage, testis, kidney, endometrium, uterus, bladder, spleen, thymus, thyroid, brain, neuron, gall bladder, ocular, and joint tissues.

29. **(Withdrawn)** The method of Claim 23, wherein said contacting is *in vitro*.

30. **(Withdrawn)** The method of Claim 23, wherein said contacting is *in vivo* in a non-human mammal.

31. **(Withdrawn)** A method for isolating hematopoietic progenitor cells from a tissue, comprising:

a) providing:
   i) a tissue comprising hematopoietic progenitor cells, and
   ii) an antibody that specifically binds to integrin $\alpha4\beta1$,

b) treating said tissue with said antibody under conditions such that said antibody specifically binds to said integrin $\alpha4\beta1$, and

c) isolating the integrin $\alpha4\beta1$ that binds to said antibody, thereby isolating said hematopoietic progenitor cells.

32. **(Previously presented)** The method of Claim 1, wherein said target tissue comprises vascular endothelial tissue.

33. **(Previously presented)** The method of Claim 15, wherein said angiogenic disease is selected from the group consisting of neoplastic disease, diabetic retinopathy, macular degeneration, psoriasis hemangiomas, gingivitis, rheumatoid arthritis, osteoarthritis, inflammation, and inflammatory bowel disease.

REMARKS

1. STATUS OF THE CLAIMS

Claims 1-33 are pending, of which Claims 23-31 were previously withdrawn by the Examiner as being directed to a non-elected invention.[1]

2. WITHDRAWN REJECTION

Applicant notes, with appreciation, that the Examiner withdrew the prior rejection of Claims 1-22, 32 and 33 under 35 U.S.C. §112, first paragraph, on the basis that the step of "detecting altered level of HPC adhesion" allegedly constitutes new matter,[2] since this rejection has not been reiterated in the instant Office Action.

3. REJECTION OF CLAIMS 1-22, 32 AND 33 UNDER 35 U.S.C. §102(b) OVER PAPAYANNOPOULOU *et al.* (WO 94/11027)

The Examiner continued to reject Claims 1-22, 32 and 33 under 35 U.S.C. §102(b) for alleged anticipation by Papayannopoulou *et al.* (WO 94/11027).[3] Applicant respectfully traverses because Papayannopoulou *et al.* fails to disclose, both expressly and inherently, the limitations of step c) of the claims, and because alleged inherency is rebutted by the enclosed Declaration by Dr. Cheresh. This is further discussed below.

A. Papayannopoulou *et al.* fails to expressly disclose the recited step c)

Express anticipation is lacking because Papayannopoulou *et al.* fails to expressly disclose the recited step c). Under the law,

> "Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration."[4] The corollary to that holding is that "absence from the reference of any claimed element negates anticipation."[5]

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1 Prior Office Action mailed 8/25/2009, page 2, 3rd paragraph.
2 Prior Office Action mailed 4/19/2011, page 4, item #6.
3 Office Action, page 2, item #4.
4 *W.L. Gore & Assoc., Inc v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 172 (1984), citing *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 960, 148 USPQ 298, 301, adopted, 149 USPQ 640 (Ct. Cl. 1966).

Applicant previously argued that Papayannopoulou *et al.* anticipates only if it discloses each of the steps of the rejected claims, including step c) of "detecting an altered level of adhesion of said hematopoietic progenitor cells to said target tissue that is not bone marrow endothelial tissue." Applicant also previously argued, and the enclosed Declaration by Dr. Cheresh (paragraph #4) confirms, that this is **not** the case here because "Papayannopoulou *et al.*'s methods relate to a different tissue (*i.e.*, **bone marrow**) from the instantly recited tissue that is "**not bone marrow** endothelial tissue." Since Papayannopoulou *et al.* is conspicuously silent on the recited step c), this precludes express anticipation.

The Examiner responded that "the instant specification does not provide a clear definition for the term 'detecting an altered levels of adhesion'"[6] and that "when the phrase 'detecting an altered levels of **adhesion**' is given its broadest reasonable interpretation in light of the specification, it can read on detecting **peripheralization** as taught by WO' 027."[7]

However, the Examiner's equation of the invention's "adhesion" with Papayannopoulou *et al.*'s "peripheralization" suffers from at least two problems.

First, the Examiner's assertion is an improper statement that stands unsupported by evidence or reasoning. MPEP 706.03 directs the Examiner that

> "Where a major technical rejection is proper (e.g., lack of proper disclosure, undue breadth, utility, *etc.*) such rejection should be stated with a full development of the **reasons** rather than by a mere conclusion coupled with some stereotyped expression."[8]

Since the Examiner's assertion is improperly unsupported by reasoning, the Examiner is respectfully requested to withdraw this line of argument.

Second, the Examiner's assertion is contradicted by the understanding of one of ordinary skill in the art. In particular, the enclosed Declaration by Dr. Cheresh (paragraph #5.C.) avers that based on the

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5 *Rowe v. Dror*, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997), citing *Kloster Speedsteel AB v. Crucible, Inc.*, 793 F.2d 1565, 1571, 230 USPQ 81, 84 (Fed. Cir. 1986).

6 (Emphasis added) Office Action, page 2, last full paragraph.

7 (Emphasis added) Office Action, page 3, 1st paragraph.

8 Emphasis added.

> ". . . teachings of the specification, prior art cited therein, and on Papayannopoulou *et al.*, it is my understanding that the claimed invention's cell-to-cell "**adhesion**" is a **different phenomenon** from Papayannopoulou *et al.*'s "**peripheralization**." In particular, the recited "adhesion" of HPCs refers to the **binding** of an extracellular domain of its integrin $\alpha4\beta1$ membrane protein with a second molecule that is on the surface of another cell type, which is in contrast to Papayannopoulou *et al.*'s "peripheralization" of HPCs that means **releasing** these cells into the peripheral blood."

In view of the above, the Examiner's assertion in equating the invention's "adhesion" with Papayannopoulou *et al.*'s "peripheralization" is contradicted by the understanding of one of ordinary skill in the art of these two terms. Accordingly, the Examiner's assertion cannot properly form the basis of anticipation of the claims by Papayannopoulou *et al.*

B. **<u>The Examiner has failed to meet their burden of establishing Inherency of the recited step c), and improperly ignores this limitation of the claims</u>**

The Examiner continues to allege anticipation under the doctrine of inherency by arguing that Papayannopoulou *et al.* "does not limit [*sic.*] its method only to bone marrow endothelial tissue" because its methods "would **inherently** result in treating various target tissue that expressed integrin $\alpha4\beta1$."[9] However, this argument improperly ignores the claims' limitation of the recited **active step c)** of **"detecting"** an altered level of adhesion of hematopoietic progenitor cells to target tissue that is "not bone marrow endothelial tissue."

Under the law,

> "In relying upon the theory of inherency, the Examiner must provide a **basis in fact and/or technical reasoning** to reasonably support the determination that the allegedly inherent characteristic **necessarily flows** from the teachings of the applied prior art."[10]

> "To establish inherency, the extrinsic **evidence** 'must make clear that the missing descriptive matter is **necessarily present** in the thing described in the reference, and that

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[9] Office Action, page 3, 2nd paragraph.

[10] (Emphasis added) MPEP 2112, citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int. 1990).

it would be so recognized by persons of ordinary skill.'"[11] "Inherency, however, **may not be established by probabilities or possibilities**. The mere fact that a certain thing **may** result from a given set of circumstances is **not sufficient**."[12]

In other words, it is **the Examiner's burden** when arguing anticipation under the doctrine of inherency to provide "**evidence**" and/or "**technical reasoning**" that Papayannopoulou *et al.* **actively** carried out the recited **active step c)** of "**detecting**" an altered level of adhesion of hematopoietic progenitor cells to target tissue that is "not bone marrow endothelial tissue."

The Examiner has failed to meet his burden because none the Examiner's arguments relates to **this particular** step. Rather, the Examiner refers only to a **different phenomenon**, namely to "**treating** various target tissue that expressed integrin $\alpha 4\beta 1$."[13] It is irrelevant to the inherency inquiry whether Papayannopoulou *et al.* inherently treats various target tissue that expressed integrin $\alpha 4\beta 1$; what **is relevant** is evidence and/or technical reasoning demonstrating whether Papayannopoulou *et al.*'s methods **necessarily** include carrying out the recited **active step** c) of "**detecting**" an altered level of adhesion of hematopoietic progenitor cells to target tissue that is "not bone marrow endothelial tissue." Since the Examiner has failed to meet their burden by neglecting to provide any such evidence and/or technical reasoning, inherency is not established. Therefore, the claims are not anticipated.

C. **Alleged Inherency of step c) is rebutted**

The enclosed Declaration by Dr. Cheresh (item #6) rebuts any allegation of inherency. The Declaration avers that step c) was not "necessarily" included in the methods of Papayannopoulou *et al.* because

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11 (Emphasis added) *In re Robertson*, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999), citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

12 (Emphasis added) *In re Robertson*, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999), *citing Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPPQ 323, 326 (CCPA 1981); see also, *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995), rehearing denied, in banc suggestion declined (Jun 21, 1995).

13 Office Action, page 3, 2nd paragraph.

"Prior to the instantly claimed invention, the prior art was **ignorant** of a role of integrin $\alpha 4\beta 1$ that is expressed on HPCs in the recited "**adhesion**" of these cells to "target tissue that is not bone marrow endothelial tissue." In view of this ignorance, it is my opinion that there is no scientific argument that would logically demonstrate that Papayannopoulou *et al.* actively carried out the recited step of "detecting" the level of a **hitherto unknown phenomenon**, *i.e.*, the recited phenomenon of "adhesion of said hematopoietic progenitor cells to said target tissue that is not bone marrow endothelial tissue."

In view of this, alleged anticipation under the doctrine of inherency is rebutted.

In summary, Papayannopoulou *et al.* cannot anticipate because it fails to disclose, both expressly and inherently, the limitations of step c) of the claims. Furthermore, alleged inherency is rebutted by the enclosed Declaration by Dr. Cheresh. In view of this, Applicant respectfully requests that the Examiner withdraw the rejection of Claims 1-22, 32 and 33 under 35 U.S.C. §102(b) over Papayannopoulou *et al.*

CONCLUSION

Applicant respectfully requests reconsideration of the application in view of the above, which places the claims in condition for allowance. To expedite prosecution, Applicant also respectfully invites the Examiner to **call the undersigned before drafting another written communication**, if any.

The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. **08-1290**.

Dated: December 20, 2011

Respectfully submitted,
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